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Randomized, placebo-controlled trial of the effects of drospirenone-estradiol on blood pressure and potassium balance in hypertensive postmenopausal women receiving hydrochlorothiazide

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Abstract

Objective: Drospirenone (DRSP), a spironolactone analog with aldosterone antagonist activity, is a novel progestogen developed for use as hormone therapy in postmenopausal women in combination with 17β-estradiol (E_2). DRSP/E_2 lowers blood pressure when used alone in hypertensive postmenopausal women or when administered concomitantly with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. DRSP/E_2 has not been studied in combination with the widely prescribed hydrochlorothiazide (HCTZ). We investigated the effects of 3 mg DRSP/1 mg E_2 versus placebo on blood pressure and potassium balance when added to existing therapy with 25 mg HCTZ in postmenopausal women with established stage I hypertension.

Design: This was a single-center, double-blind, randomized, placebo-controlled, two-treatment, two 4-week treatment period crossover study in 36 postmenopausal women with stage I hypertension maintained on 25 mg HCTZ. The endpoint was a change from baseline in systolic and diastolic blood pressures by 24-hour ambulatory blood pressure monitoring. Safety monitoring included serum potassium (mEq/L) and adverse events.

Results: Mean systolic and diastolic blood pressures by 24-hour ambulatory blood pressure monitoring were reduced significantly, by −7.2 and −4.5 mm Hg, respectively, with DRSP/E_2 as compared with placebo. The decrease in potassium with HCTZ was 0.2 mEq/L less with DRSP/E_2 than placebo, suggesting a potassium-sparing effect. The most frequently observed adverse events with DRSP/E_2 were vaginal bleeding and breast tenderness, which were attributable to the hormone therapy.

Conclusions: DRSP/E_2 substantially lowers systolic and diastolic blood pressure when added to existing antihypertensive therapy with HCTZ in hypertensive postmenopausal women. In addition, DRSP/E_2 has a potassium-sparing effect that counteracts HCTZ-induced potassium loss.

Key Words: Hormone therapy – Hypertension – Drospirenone – Aldosterone – Aldosterone antagonists – Progesterone – Progestogens – Hydrochlorothiazide – Potassium – Diuretics – Drug interactions.

Hypertension is a major risk factor for cardiovascular disease and stroke and is increasing in prevalence.[1-7] Despite the profound benefits offered by the pharmacological treatment of hypertension,[3-7] hypertension is inadequately treated or not treated at all in the majority of patients.[1,4-6] It is estimated that only 68.9% of those with hypertension in the United States are aware of their diagnosis, 58.4% are treated, and only 31.0% of hypertensives are at goal blood pressure.[1] This shortcoming of medical intervention contributes to an enormous burden of excess morbidity and mortality and utilization of costly healthcare resources.

The years proximate to menopause are accompanied by an increase in blood pressure and an increasing prevalence of hypertension.[1,4,5,8-11] This increase in blood pressure may partially explain the corresponding marked and progressive increased risk of cardiovascular events observed in postmenopausal women. It is clear that novel and alternative treatment strategies aimed at reducing cardiovascular risk in postmenopausal women are warranted.

Drospirenone (DRSP), a spironolactone analog, is a novel progestogen with aldosterone antagonist activity. DRSP has been developed for use in postmenopausal women as hormone therapy (HT) in combination with 17β-estradiol (E_2).[12-18] Several recent clinical trials have uniformly demonstrated that DRSP/E_2 lowers blood pressure in hypertensive postmenopausal women.[18-22] Furthermore, DRSP/E_2 has an

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additive effect on blood pressure when administered in combination with existing antihypertensive therapy with angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists.[19,20]

Hydrochlorothiazide (HCTZ) has been widely recommended as an appropriate first-line therapy for hypertension.[4,5,23,24] Whether there is a further blood pressure– lowering effect of DRSP/E_2 when added to ongoing HCTZ therapy has not been tested. In addition, HCTZ therapy has been associated with renal potassium loss and a decrease in serum potassium concentration in some patients. Because DRSP has aldosterone antagonist activity, it is possible that it may have a potassium-sparing effect when given in combination with HCTZ. The objective of this investigation was to determine the effects on 24-hour ambulatory blood pressure, potassium balance, and safety when 3 mg DRSP/1 mg E_2 is given to hypertensive postmenopausal women receiving concomitant therapy with HCTZ 25 mg/day.

METHODS

The study protocol was approved by and conducted in accordance with the guidelines of the University of Miami Institutional Review Board and the Western Institutional Review Board. Study personnel obtained written informed consent directly from all women before their entry into the study. The study was conducted in accordance with Good Clinical Practices and International Council on Harmonization guidelines. Study medication (DRSP/E_2, HCTZ, and placebo) were supplied by Berlex Laboratories, Inc.

Study objectives

The objectives of this study were to determine the effects of a 4-week treatment period of DRSP/E_2 versus placebo on blood pressure, serum potassium, HCTZ pharmacokinetics, and safety profile when added to existing therapy with 25 mg HCTZ. The primary endpoint was mean 24-hour ambulatory blood pressure. Safety parameters included recording of adverse events (AEs) and monitoring of serum potassium. The secondary endpoint was pharmacokinetics of HCTZ at baseline and at week 4 of each treatment period. We report here the results of the blood pressure, AEs, and potassium data. The detailed pharmacokinetic analysis will be presented elsewhere.

Study design

The study was performed as a single-center, double-blind, randomized, placebo-controlled, two-treatment (DRSP/E_2 vs placebo), two 4-week treatment period crossover study in 36 postmenopausal women with stage I hypertension maintained on 25 mg HCTZ. The study design is summarized in Figure 1. The two study treatments were DRSP/E_2 (containing 3 mg DRSP/1 mg E_2) and matching placebo tablets.

The crossover study was composed of four periods (Fig. 1): a 2- to 5-week screening/washout period, followed by a 3-week open-label HCTZ run-in period. HCTZ was continued throughout the remainder of the study. The 3-week open-label HCTZ run-in period was followed by treatment period 1 for 4 weeks (either DRSP/E_2 or placebo), a 3-week washout period, and the 4-week treatment period 2 (either placebo or DRSP/E_2). Clinic visits were scheduled at 1-week (5- to 7-day) intervals.

Study participants were randomly assigned to treatment sequence 1 or treatment sequence 2. Eighteen participants received treatment sequence 1, and 18 participants received treatment sequence 2. In treatment sequence 1, the women received placebo and 25 mg HCTZ for the 4 weeks of treatment

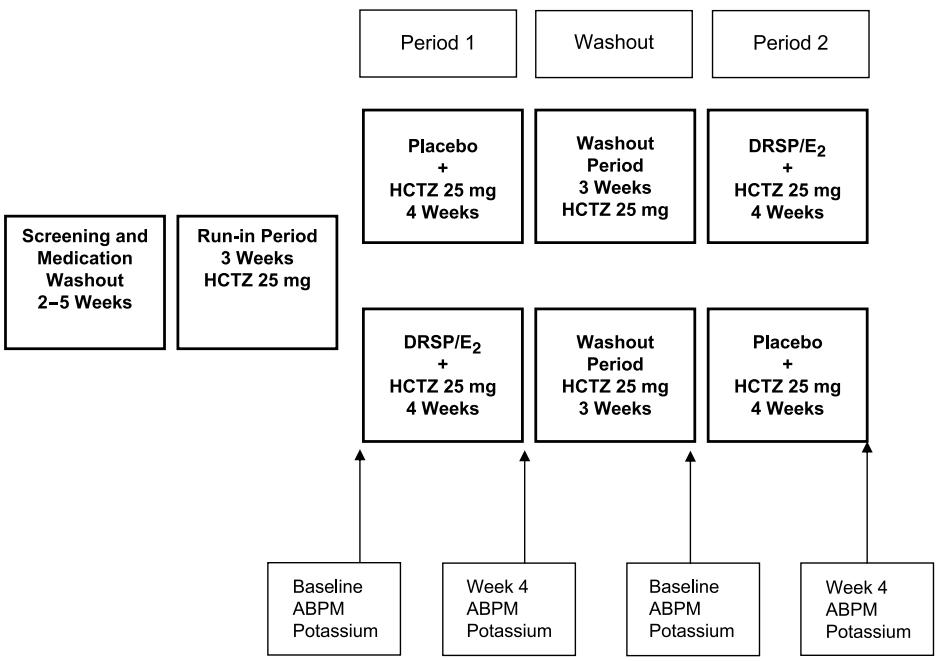

FIG. 1. Study design. DRSP, drospirenone; E_2, 17β-estradiol; HCTZ, hydrochlorothiazide, ABPM, ambulatory blood pressure monitoring.

period 1, a 3-week washout period during which they received only 25 mg HCTZ daily, and then DRSP/E_2 and 25 mg HCTZ for the 4 weeks of treatment period 2. In treatment sequence 2, the order of treatment was reversed: women received DRSP/E_2 and 25 mg HCTZ for the 4 weeks of treatment period 1, a 3-week washout period, and then placebo and 25 mg HCTZ for the 4 weeks of treatment period 2.

Treatments (DRSP/E_2 or matching placebo) were given once daily in the morning for 4 weeks during each of the two treatment periods. Medication was taken at the study center on visit days after all assessments.

Study population

Each woman was required to meet the following criteria: 40 to 75 years of age; stage I hypertension determined during the screening/washout period: systolic blood pressure (SBP) 140 to 159 mm Hg and diastolic blood pressure (DBP) 90 to 99 mm Hg; natural or surgical menopause; serum E_2 levels less than or equal to 20 pg/mL and serum follicle-stimulating hormone (FSH) levels greater than or equal to 40 mIU/mL; normal gynecological examination, including pelvic and breast examinations and a mammogram; cervical smears (nonhysterectomized women) or vaginal smears (hysterectomized women) performed with nonclinically significant results; serum potassium at screening in the normal range (3.5-5.3 mEq/L); and screening creatinine clearance estimated from serum creatinine greater than 50 mL/min by the Cockcroft-Gault formula.[25]

Women were excluded from the study if there was a history of unstable concomitant medical illness, secondary cause of hypertension, unstable blood pressure, smoking more than 10 cigarettes per day, drug or alcohol abuse, abnormal cervical smear or mammogram; clinically significant abnormal laboratory values or electrocardiogram abnormalities; previous diagnosis of cancer of any type; or known sensitivity to study medication.

Study procedures

Ambulatory blood pressure monitoring (ABPM)

ABPM measurements were performed in all women to monitor the effect of the treatments during a 24-hour interval at baseline and after 4 weeks of treatment with either DRSP/E_2 or placebo. ABPM was performed using a Spacelabs 90207 device. The ABPM measurements of each woman were performed on the nondominant arm, and women were instructed to keep their arm as still as possible during the actual recordings of blood pressure. Showering and strenuous exercise were not allowed while the ABPM device was worn. Study drug was given immediately after the first ABPM recording had taken place. ABPM measurements were automatically recorded at 15-minute intervals during daytime (6:00 AM to 9:59 PM) and at 20-minute intervals during nighttime (10:00 PM to 5:59 AM).

Serum potassium

Serum potassium was measured at screening, once every week during the 3-week HCTZ run-in period, at baseline before each of the two treatment periods (DRSP/E_2 or placebo), and weekly during each of the treatment periods. Mean serum potassium change from baseline to week 4 of each of the two treatment periods (DRSP/E_2 vs placebo) were compared. In addition, the number of women with serum potassium less than or equal to 3.2 mEq/L and greater than or equal to 5.5 mEq/L were compared.

Safety measurements

Safety was evaluated by the use of history, participant reporting, physical examination at scheduled visits, vital signs, clinical laboratory test results, and collection of AE data.

Statistical methods

The sample size estimation was based on the one-sided, $\alpha = 0.025$ level test procedure described below for the primary variable, mean systolic 24-hour ABPM. In an earlier study of 3 mg DRSP/1 mg E_2 in hypertensive postmenopausal women, the observed difference of the changes in SBP was -9 mm Hg.[19] To estimate the sample size for this study, it was assumed that the difference in the change in SBP between the two treatments would be less than -4.5 mm Hg. Noninferiority could be tested with a power of 80%. A total of 24 assessable women (12 per sequence) was estimated to be required to demonstrate a difference between the two treatments. Given the length of the study and anticipating dropouts, 36 women were randomized. The primary efficacy variable was the mean change from baseline in systolic 24-hour ABPM at 4 weeks. The test for noninferiority was performed using analysis of variance with factors of sequence (fixed with two levels), participant (random nested in sequence), treatment (fixed with two levels of test and placebo), and period (fixed with two levels). The two-sided 95% CI was constructed for the treatment difference (ie, DRSP/E_2 − placebo). The null hypothesis was rejected and noninferiority concluded if the upper limit of the CI was less than the defined noninferiority margin (ie, 2 mm Hg). This procedure is equivalent to the one-sided test at a significance level of 0.025.

RESULTS

All 36 participants were female, ranging in age from 50 to 74 years (Table 1). Most women (58%) were Hispanic, with

TABLE 1. *Demographic and screening characteristics*

Variable	Total group (N = 36)
Age	61.2 (6.6)
Race/ethnicity, n (%)	
African American	9 (25%)
White	6 (17%)
Hispanic	21 (58%)
Weight, kg	77.8 (14.1)
Body mass index, kg/m^2	31.1 (5.6)
Age at last menstruation	48.5 (5.7)
Screening systolic BP, mm Hg	138 (7.08)
Screening diastolic BP, mm Hg	84.6 (4.07)
Screening potassium, mEq/L	4.13 (0.37)
Creatinine clearance, mL/min	85.9 (24.1)

Values are mean (SD) unless noted otherwise. BP, blood pressure.

black and white women comprising 25% and 17%, respectively. Mean body weight was 77.8 kg, and mean body mass index was 31.1 kg/m^2. Demographic and screening characteristics are displayed in Table 1.

Of the 58 women screened for this study, 22 (23%) were excluded. Twelve women had abnormal mammogram and/or Pap smear results, 10 had abnormal laboratory test results, and 7 did not meet criteria for hormone levels. One woman had breast cancer, and another had a positive urine drug screen. Several women had more than one reason for exclusion. During screening, no woman was excluded from the study due to serum potassium. A total of 36 women were randomized (18 women per treatment sequence), treated, and completed the study. No women prematurely discontinued the study medication or were prematurely discontinued during study treatment periods.

Mean 24-hour ABPM

The mean systolic 24-hour ABPM was comparable for the DRSP/E_2 and placebo treatments at baseline (133.4 and 132.2 mm Hg, respectively). At week 4, the mean change from baseline values decreased to a greater extent in the DRSP/E_2 treatment than in the placebo treatment (−7.6 and −0.4 mm Hg, respectively), with a mean difference between DRSP/E_2 and placebo of −7.20 mm Hg (Fig. 2).

The two-sided 95% CI for the mean change in SBP treatment difference (DRSP/E_2 − placebo) was −10.97 to −3.44. Because the upper limit of the CI (−3.44) is less than the predefined noninferiority margin of 2 mm Hg, the null hypothesis was rejected and noninferiority concluded.

The mean absolute diastolic 24-hour ABPM values were comparable for the DRSP/E_2 and placebo treatments at baseline (78.3 and 77.0 mm Hg, respectively). At week 4, the mean values decreased to a greater extent in the DRSP/E_2 treatment than in the placebo treatment (−4.9 and −0.4 mm Hg, respectively) with a mean difference of −4.52 mm Hg.

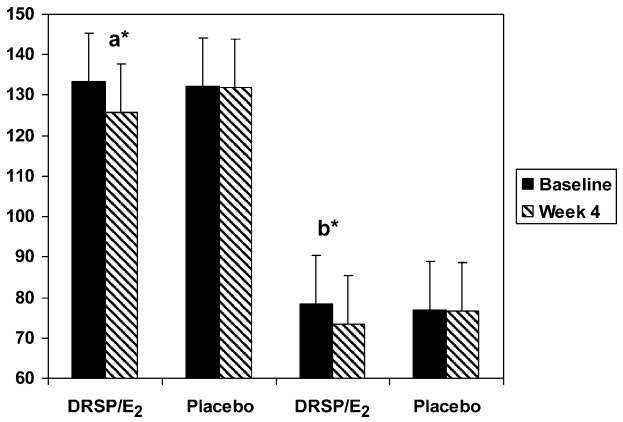

FIG. 2. 24-Hour ambulatory blood pressure monitoring of systolic and diastolic blood pressures. **a*:** Mean change from baseline in systolic blood pressure was −7.6 mm Hg (range: +8 to −27 mm Hg) for drospirenone (DRSP)/17β-estradiol (E_2) and −0.4 mm Hg (range: +16 to −15 mm Hg) for placebo. The difference in change from baseline between DRSP/E_2 and placebo in systolic blood pressure = −7.20; 95% CI: −10.97 to −3.44. **b*:** Mean change from baseline in diastolic blood pressure was −4.9 mm Hg (range: +6 to −16 mm Hg) for DRSP/E_2 and −0.4 mm Hg (range +6 to −15 mm Hg) for placebo. The difference in change from baseline between DRSP/E_2 and placebo in diastolic blood pressure = −4.2; 95% CI: −6.94 to −2.10.

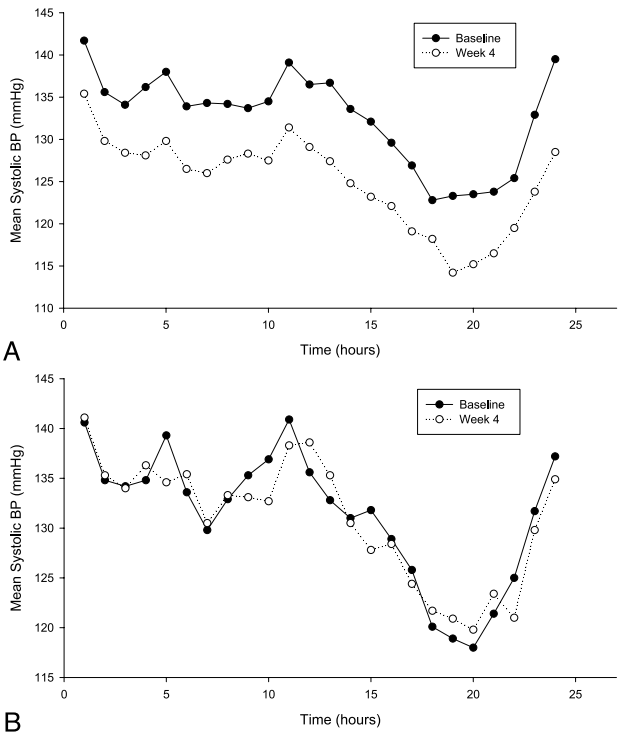

FIG. 3. Mean hourly ambulatory blood pressure monitoring (ABPM) blood pressure at baseline and week 4. **A:** Mean systolic hourly ABPM blood pressure at baseline and week 4 for the drospirenone/17β-estradiol treatment. **B:** Mean systolic hourly ABPM blood pressure at baseline and week 4 for the placebo treatment.

Daytime and nighttime ABPM

At week 4, the mean absolute daytime systolic ABPM values decreased to a greater extent in the DRSP/E_2 treatment than in the placebo treatment (−7.6 and −0.5 mm Hg, respectively), and diastolic ABPM mean values decreased to a greater extent in the DRSP/E_2 treatment than in the placebo treatment (−4.9 and −0.3 mm Hg, respectively).

Nighttime systolic and diastolic ABPM values decreased to a greater extent in the DRSP/E_2 treatment than in the placebo treatment (−7.4 vs −0.3 mm Hg and −4.7 vs −0.9 mm Hg, respectively).

Hourly 24-hour ABPM

The hourly systolic and diastolic 24-hour ABPM data for the DRSP/E_2 and placebo treatments are shown in Figures 3 and 4. DRSP/E_2 treatment resulted in consistent reductions of both SBP and DBP throughout the entire 24-hour observation period, whereas placebo was associated with no significant reduction in either SBP or DBP.

The 3-week washout between treatment periods was intended to minimize residual carryover effect from the first treatment period. At the follow-up visit (3-14 days after the last dose of study medication), mean SBP values increased toward baseline levels and were similar between the treatment groups.

Potassium

A small decline in mean serum potassium was observed during the run-in period in women maintained on 25 mg/day HCTZ. This may reflect the potassium depletion characteristic of thiazide therapy. At week 4, the mean change from baseline for the DRSP/E_2 treatment was 0.27 mEq/L and for placebo was 0.066 (Table 2). This difference was statistically significantly greater for DRSP/E_2 than for the placebo treatment ($P = 0.0059$). No study woman developed hyperkalemia during the study.

Five women had one or more serum potassium values of 3.2 mEq/L or less while receiving study drug (DRSP/E_2 or placebo) during treatment periods 1 and 2; one woman was receiving DRSP/E_2 treatment, and four women were on placebo treatment.

Safety

Few treatment-emergent AEs were experienced by women in this study. A total of 14 of the 36 women reported at least one treatment-emergent AE during the study. Twelve of the 36 women (33%) reported AEs during the DRSP/E_2 treatment, and 2 of the 36 women (6%) reported AEs during the placebo treatment.

Common AEs (occurring in 5% or more of women) during the DRSP/E_2 treatment included vaginal bleeding (eight women, 22%), breast pain (three women, 8%), and flu syndrome (two women, 6%). The only AEs during the placebo treatment were flu syndrome and chest pain (one woman, 3% for each AE). No woman developed treatment-emergent hypertension or hypotension.

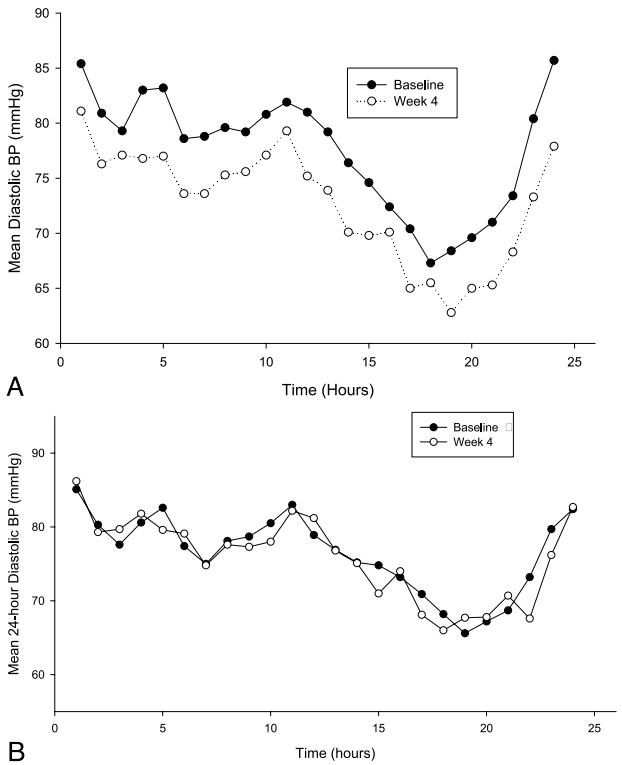

FIG. 4. Mean hourly ambulatory blood pressure monitoring (ABPM) at baseline and week 4. **A:** Mean diastolic hourly ABPM blood pressure at baseline and week 4 for the drospirenone/17β-estradiol treatment. **B:** Mean diastolic hourly ABPM blood pressure at baseline and week 4 for the placebo treatment.

TABLE 2. *Change from baseline in serum potassium*

Treatment	N	Baseline[a]	Change from baseline[b]	*P*
DRSP/E_2	36	3.92 (0.322)	0.27 (0.276)	0.0059
Placebo	36	3.96 (0.366)	0.06 (0.272)	

Values are mean (SD). DRSP, drospirenone; E_2, 17β-estradiol.
[a]Baseline serum potassium represents the average of four measurements taken at baseline.
[b]Week 4 serum potassium represents the average of seven measurements taken at week 4.

DISCUSSION

The objective of this randomized, two-treatment, two-period, placebo-controlled, crossover trial was to determine the effects of 3 mg DRSP/1 mg E_2 on 24-hour ambulatory blood pressure and potassium balance in hypertensive postmenopausal women who were receiving concomitant therapy with 25 mg/day HCTZ. The results of this investigation demonstrate clinically significant additive reductions in systolic and diastolic 24-hour ambulatory blood pressure with DRSP/E_2 compared with placebo when added to 25 mg HCTZ. We also observed a potassium-sparing effect of 3 mg DRSP/1 mg E_2, which reduced the decrease in serum potassium produced by HCTZ compared with placebo and led to fewer cases of hypokalemia.

At week 4, the mean change from baseline potassium concentration for the DRSP/E_2 treatment was 0.27 mEq/L, and for placebo it was 0.066 mEq/L (Table 2). This difference was statistically significantly greater for DRSP/E_2 than for the placebo treatment ($P = 0.0059$). The mean baseline potassium levels in our study were well within the normal range. Therefore, a change of +0.27 from the mean baseline of 3.92 mEq/L versus a change of +0.06 from the mean baseline of 3.96 mEq/L, as seen in our study, would probably be of little clinical significance. Nevertheless, a potassium-sparing effect of 0.21 mEq/L could be clinically important at low levels of serum potassium (in the range of 3.2-3.3 mEq/L, for example) caused by thiazide-induced potassium loss. Such a difference of 0.21 mEq/L could be clinically important in counteracting clinical hypokalemia.

A potential limitation of this present study could be that the study participants were predominantly of Hispanic ethnicity. Nevertheless, we consider that our results may be generalized to a broader population based on several clinical trials that have uniformly demonstrated that DRSP/E_2 lowers blood pressure in hypertensive postmenopausal women of diverse ethnicities.[18-22] The magnitude of blood pressure reduction as determined by ABPM recording in our study was similar in magnitude to that seen in other trials. Furthermore, DRSP/E_2 has an additive lowering effect on blood pressure when administered in combination with existing antihypertensive therapy with angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists.[19,20] We studied the effects

of 3 mg DRSP/1 mg E_2 on blood pressure in 230 hypertensive postmenopausal women 44 to 70 years old with type 2 diabetes mellitus (n = 82) or without type II diabetes mellitus (n = 148) on an angiotensin-converting enzyme inhibitor or angiotensin II receptor antagonist randomized to 28 days of DRSP/E_2 or placebo.[20] Ethnicity was approximately equally distributed among African American, Hispanic, and white women. Blood pressure was reduced by −8.6/−5.8 mm Hg on DRSP/E_2 versus −3.7/−2.9 mm Hg on placebo ($P < 0.01$ for both SBP and DBP), suggesting that DRSP/E_2 has a significant antihypertensive effect even in a high-risk hypertensive population.

There are clinical trial data that the blood pressure–lowering effect of DRSP/E_2 exceeds the brief 4-week treatment period of this study. The effects of 3 mg DRSP/1 mg E_2 on clinic and 24-hour ambulatory blood pressure were evaluated in 212 postmenopausal women with grade I hypertension in a 12-week multicenter, double-blind, randomized, placebo-controlled study.[21] Ethnicity was distributed as approximately 90% nonblack and 10% black. The clinic (cuff) blood pressure was reduced significantly on DRSP/E_2 (−14.1/−7.9 mm Hg for DRSP/E_2 vs −7.1/−4.3 mm Hg for placebo ($P < 0.0001$). Twenty-four-hour ambulatory blood pressure decreased by −8.5/−4.2 mm Hg versus −1.8/−1.6 mm Hg in those on placebo ($P = 0.002/0.07$).

The results of this study confirm earlier reports[18-22] that DRSP/E_2 has a significant blood pressure–lowering effect and generalize this finding to a hypertensive population that is receiving ongoing antihypertensive therapy with the widely prescribed HCTZ. The considerable reduction in ambulatory blood pressure of −7.2 mm Hg compared with placebo is consistent with our earlier results.[19-22]

This study demonstrated no adverse interactions affecting either blood pressure or potassium balance between 3 mg DRSP/1 mg E_2 and HCTZ. This is consistent with our earlier findings when 3 mg DRSP/1 mg E_2 was administered in combination with angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists.[19,20] Furthermore, 3 mg DRSP/1 mg E_2 has been shown to have a substantial blood pressure–lowering effect in high-risk patients with coexisting hypertension and diabetes mellitus.[20]

Our results confirm that DRSP/E_2 can be administered concomitantly with HCTZ. The additive effect of DRSP/E_2 on reducing blood pressure when coadministered with antihypertensive drugs has important clinical implications for the postmenopausal hypertensive patient. The first implication is that DRSP/E_2 can be considered when HT is required in a patient on antihypertensive therapy. The second implication originates from the observations from recent clinical trials that effective blood pressure control can be achieved in most patients who are hypertensive, but many patients will require two or more antihypertensive drugs.[8,9] Because DRSP/E_2 has a blood pressure–lowering effect comparable in magnitude to available antihypertensive drugs, adding DRSP/E_2 as HT may help to allow fewer antihypertensive drugs to achieve a target blood pressure.

DRSP is a spironolactone analog with aldosterone antagonist activity. In addition to the cardiovascular benefits of reducing blood pressure, aldosterone blockade may confer additional cardioprotective effects that are independent of blood pressure per se.[26-35] Several recent clinical trials demonstrate the benefit of aldosterone blockade in reducing a variety of cardiovascular and renal endpoints.[33-35] In view of the predominantly negative results of trials of standard HT on blood pressure and cardiovascular outcomes,[36-39] a novel HT with aldosterone antagonist activity could potentially offer a unique and direct mechanism for reducing blood pressure and cardiovascular risk. Hormone therapy with a combination of E_2 and DRSP, a novel aldosterone antagonist, may therefore offer a theoretical advantage in cardiovascular benefit/risk assessment in postmenopausal women.

CONCLUSION

Our study demonstrates that DRSP/E_2 produces a significant lowering of both SBP and DBP in hypertensive postmenopausal women treated with 25 mg/day HCTZ. Furthermore, we observed less decline in serum potassium and fewer cases of hypokalemia with DRSP/E_2 treatment compared with placebo, suggesting a beneficial potassium-sparing effect of DRSP/E_2. The favorable effects on blood pressure and the aldosterone antagonist activity of DRSP/E_2 may commend its preferential use as HT in postmenopausal women.

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